Post-cardiotomy extracorporeal cardiopulmonary resuscitation in neonates with complex single ventricle: analysis of outcomes☆

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Abstract

Objective: Extracorporeal cardiopulmonary resuscitation (ECPR) in children with cardiac arrest refractory to conventional cardiopulmonary resuscitation (CPR) has been reported with encouraging results. We sought to review outcomes of neonates with functional single ventricle (FSV) receiving post-cardiotomy ECPR. Methods: Forty-eight patients who required post-cardiotomy extracorporeal membrane oxygenation (ECMO) since the introduction of our ECPR protocol (January 2007–December 2009) were identified. Twenty-seven were neonates. Review of records and survival analysis were conducted. Results: Of 27 neonates receiving post-cardiotomy ECMO 20 had FSV. Fourteen had ECPR. Ten underwent Norwood operation (NO) for hypoplastic left heart syndrome (HLHS). Four had FSV other than HLHS. Three underwent Damus–Kay–Stansel or modified NO with systemic-to-pulmonary shunt (SPS) and one SPS with anomalous pulmonary venous connection repair. Mean age and weight were 7.8 ± 2.9 days and 3.44 ± 1.78 kg, respectively. ECMO median duration was 6 days (interquartile range (IQR) 3–14). Survival to ECMO discontinuation was 79% (11 of 14 patients) and at hospital discharge was 57% (8 of 14 patients). The most common cause of death was multi-organ failure (four of six deaths). At last follow-up (median: 11 months (1–34)) 43% of patients were alive. CPR mean duration for patients with favorable versus unfavorable outcome was 38.6 ± 6.3 versus 42.1 ± 7.7 min (p = 0.12). Previously reported determinants for poorer prognosis in conventional non-rescue ECMO (such as pre-ECMO pH < 7.2, renal, neurological or pulmonary hemorrhage complications, and pre- and post-vasoactive inotropic score) did not influence outcome between survivors and non-survivors (p > 0.05). Conclusions: ECMO support in neonates with FSV requiring ECPR can result in favorable outcome in more than half of patients at hospital discharge. Aggressive strategy toward timely application of ECPR is justified. Expeditious ECPR deployment after proper patients’ selection, refinement of CPR quality and use of adjunctive neuroprotective interventions, such as induced hypothermia, might further improve outcomes.

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Keyword: Extracorporeal cardiopulmonary resuscitation

1. Introduction

Use of extracorporeal membrane oxygenation (ECMO) after surgical correction of congenital heart defects (CHDs) has continued to steadily increase. Since the first [1] reported use of ECMO after CHD palliative repair, it has been widely used for resuscitation after cardiac operations in children. There are no widely established criteria governing its use and results varied [2–8]. The ELSO registry [7] and others [8] indicate that ECMO after repair of functional single ventricle (FSV) has poorer prognosis than other cardiac lesions with increased short-term neuromorbidity. Prolonged conventional cardiopulmonary resuscitation (CPR) is reportedly associated with extremely poor survival [2–7]. Increased duration of CPR in neonates and infants with hospital cardiac arrest carries substantial morbidity and high mortality [2–7]. Extracorporeal cardiopulmonary resuscitation (ECPR) is the rapid deployment of ECMO to provide immediate cardiovascular support for patients, who have cardiac arrest refractory to conventional CPR strategies [3,9]. Survival after ECPR in pediatric post-cardiotomy patients varies and results are steadily improving in the last decade [9–16]. With appropriate patient selection and institutional effectiveness to deploy ECMO in a timely fashion, rescue ECMO may influence outcome [9–16]. Since 2007, we have encountered post-cardiotomy neonates with FSV of any type for which our established ECPR protocol using a pre-assembled and pre-primed ECMO...
circuit was used. We sought to review the records of neonates with FSV receiving post-cardiomyotomy ECPR and explore determinants of outcome.

2. Patients and methods

The Heart Institute for Children’s database was analyzed. Forty-eight patients, who required post-cardiomyotomy ECMO since the introduction of our ECPR protocol (January 2007—December 2009), were identified. Of 27 neonates receiving post-cardiomyotomy ECMO, 20 had FSV. Fourteen had ECPR. One patient had additional ECMO run during the same admission. Only information from the initial ECPR run was analyzed.

Patients were included in the ECPR group, if venaarterial ECMO was used as part of the initial active resuscitation from a cardiac arrest. Patients, who were hemodynamically unstable, and in whom ECMO was urgently deployed, but without active cardiac arrest, were excluded. A retrospective analysis of demographic, clinical, and outcome data was conducted and survival analysis undertaken. ‘ECPR survivors’ indicated patients who are still alive at last follow-up.

Vasoactive inotrope score (VIS) was calculated (first 24 h from event) using the formula as originally described by Wernovsky and expanded by Gaies et al. [18]:

\[
\text{VIS} = \text{dopamine} + \text{dobutamine} + (\text{epinephrine} \times 100) + (\text{milrinone} \times 10) + (\text{vasopressin} \times 100), \quad \text{all in} \quad \mu g \text{kg}^{-1} \text{min}^{-1} (\text{except vasopressin U kg}^{-1} \text{min}^{-1}).
\]

Each patient’s VIS was classified as: (1) class-I: \(< 10\), (2) class-II: 11—14, (3) class-III: 15—19, (4) class-IV: 20—24, and (5) class-V: \(\geq 25\). FSV systolic function was qualitatively evaluated by apical and parasternal short axis images as (RVNSL) normal shortening function (SF) without myocardial wall dysfunction (RVNSL-1), mild-to-moderate myocardial wall dysfunction and reduced SF (up to 50% of normal), and (RVNSL-2) severe myocardial wall hypokinesia and severely reduced SF (more than 50% of normal). All echocardiograms were reviewed by an independent echocardiographer blinded to the study.

The study was approved by the Institutional Review Board. Need for parental consent was waived.

2.1. ECMO rapid deployment: development, strategy, and intensive care unit management

ECPR protocol was created to expedite the process of rapid ECMO deployment in patients, who experienced cardiac arrest intractable to standard CPR strategies. Its role, indications and mode of deployment remained constant throughout the study. Its aim was to reestablish cardiac output and organ perfusion to prevent permanent end-organ injury while awaiting reversal of cardiac and other organ disease process or as a bridge to heart transplantation. A team of skilled and trained professionals with well-defined individual roles and responsibilities have been identified. A certified ECMO specialist and/or cardiovascular perfusionist are available in-house at all times. Disciplines involved include cardiovascular surgeons, intensive care unit (ICU) specialists, cardiology staff, operating room (OR) staff, and cardiac nursing. Additional support includes, but is not limited, to hematology, respiratory therapy, and blood-bank and social-work specialists. Only patients under the direct care of the cardiovascular team or with recent care provided by that team can be deemed ECPR candidates. If a post-cardiomyotomy patient is deemed to be at higher risk for needing ECMO, the patient is labeled as ‘ECMO watch’. ECPR roles are assigned in advance and ECMO specialists are notified. Equipments related to ECMO deployment are ready at the bedside and the blood bank is notified accordingly. All codes in the Pediatric Surgical Heart Unit (PSHU) are currently treated as ECPR potential case.

A unique feature of our protocol is assigning roles to four nurses once ECPR is initiated. Each nurse assigned to a task is to complete it before moving on to any other. Role assignment is determined by the charge nurse as defined below:

1. The ‘call’ nurse is responsible for notifying the: (a) cardiovascular (CV) surgeon, (b) perfusionist and ECMO specialist on call, (c) OR team, (d) blood bank, (e) pediatric ICU Charge and Transport team, and (f) family.
2. The ‘equipment’ nurse is responsible for: (a) bringing the ECMO cart to the bedside, (b) transporting the MD headlamp in the room, (c) getting hats and masks for all staff unit members, and (d) cooling the room and packing the patient’s head in ice.
3. The ‘circuiting’ nurse is responsible for: (a) positioning the patient, (b) getting the Emergency bag from the ECMO cart, (c) giving the CPR nurse a sterile gown and gloves to prepare and take over CPR while that CPR nurse gets sterile, (d) removing the chest dressing (if present), and (e) performing surgical prepping and draping of the neck and chest.
4. The ‘Scrub’ nurse is responsible for: (a) checking the integrity of draping and ensuring sterility, (b) opening the ECMO cart in a sterile fashion, and (c) helping with CPR until the surgeon arrives.

Expeditious response of the ECPR deployment is contingent to the proficiency and accuracy of the team. Intense training, continuous didactic sessions, and periodic simulation strategies with rescue ECMO drills in the ICU may identify system deficits and improve delivery and response times in critical situations. Educational sessions are done on a monthly basis.

A pre-assembled and pre-primed ECMO circuit and trained personnel are available in the PSHU at all times. The circuit is composed of 1/4-in. internal diameter polyvinyl chloride tubing with Carmeda (Medtronic, Minneapolis, MN, USA) heparin-bonded biocompatible surface coating. Total prime is approximately 250 ml. The main components are the Cobe/ Sorin Revolution centrifugal pump and Quadrox-ID pediatric oxygenator (Maquet, Germany). This system can support patients up to 20 kg in weight. The circuit is primed with Plasmalyte 148 (Baxter Corp, Toronto, Canada), an unbuffered electrolyte solution, and is usable for 30 days.

Once ECPR is required, the predefined protocol is initiated as above. The cannulation site is dependent on the clinical situation. In general, the transthoracic route is used for patients requiring emergency ECMO in the immediate postoperative period. In patients who have cardiac arrest in settings other than the early postoperative period, neck cannulation is performed.
When ECPR is requested, the blood bank is notified to prepare blood products as above. Heparin 1 U ml⁻¹ of prime, sodium bicarbonate 15 mEq, and calcium chloride 250 mg are added to the prime before cannulation. Systemic heparin is administered at a dose of 50 U kg⁻¹ to maintain an activated clotting time (ACT) of 140—160 s. For a minimum of 6 h, the ACT is maintained between 140 and 160 s. If risk for post-ECMO hemorrhage is decreased, heparin infusion is administered for ACT between 160 and 180 s during the first 24 h. At 24 h, ACT is increased for the target range between 180 and 200 s and up to 200—220 s by 48 h following ECMO institution. Platelets, fresh-frozen plasma, and cryoprecipitate are given to correct the inherent coagulation deficiency. The administration of blood products continues until transfusion goals are reached: hemoglobin >12 mg l⁻¹, platelet count >100 000 mm⁻³, and fibrinogen >150 mg l⁻¹.

When pump flow is started, initially at 100 ml kg⁻¹ min⁻¹, appropriate adjustments are made to maintain end-organ perfusion, normalize arterial blood gases, minimize pulmonary overcirculation, improve regional oxygen delivery, promote clearance of lactic acidosis, and provide time for myocardial recovery. This is especially critical in a patient population with single-ventricle physiology. To prevent injury to the pulmonary vascular endothelial cell function (in the absence of antegrade pulmonary blood flow), our principle strategy favors open systemic-to-pulmonary shunt during ECMO support. Often, higher pump flows (usually >150 ml kg⁻¹ min⁻¹) are needed to compensate for the significant shunt runoff. Vasoactive-inotropic support is maintained and adjusted as needed to maintain heart function and pulsatility. Nitric oxide is delivered at 20 ppm during ECMO. The mechanical ventilatory support is titrated according to the amount of extracorporeal support in the light of single-ventricle physiology. Rate and tidal volume are accordingly adjusted to maintain oxygenation of blood generated by the native cardiac output and to prevent lung atelectasis. Gas flow and blender on the ECMO circuit are used complementary to the ventilator support to keep the blood gas values within acceptable range for single-ventricle physiology.

Continuous monitoring of bifrontal cerebral and somatic near-infrared spectroscopy (regional oxygen saturation, rSO₂) is used to help adjusting pump flow and inotropic support to maintain optimal oxygen delivery/extraction and adequate end-organ perfusion after ECMO deployment.

Once the patient is on pump, a loading 10 mg kg⁻¹ dose of phenobarbital is administered. Frequent neurological evaluation is performed every hour for 12 h after ECPR, aiming to identify persistent severe neurologic insult requiring withdrawal of ECMO support. Mild core cooling and application of ice to the patient’s head for a core temperature of 35—35.5 °C is practiced. After the initial 24 h, the patient is slowly rewarmed, not to exceed 36.5 °C, at nearly 48 h after ECMO support was initiated. Follow-up and future analysis of this strategy are needed to confirm its benefit. Head ultrasounds are done within the first 12 h on ECMO, and daily thereafter.

When urine output falls below 1 ml kg⁻¹ h⁻¹, diuretics are started to promote diuresis. If the patient remains oliguric or anuric for >6—8 consecutive hours ultrafiltration (Minntech HPH 400; Minntech, Minneapolis) is used to augment fluid balance goal. Hemodialysis is selectively used in patients with renal insufficiency.

Broad-spectrum antibiotics are prophylactically administered with an open chest, and dosage is adjusted as needed.

Follow-up echocardiography is done within 24 h, daily for 72 h, and periodically thereafter to estimate cardiac recovery, detect residual lesions, and to assess the need for heart transplantation (HTxP) in case of failure of heart recovery.

Timing of weaning is dependent on the clinical scenario, hemodynamic stability during ECMO support, correction of the underlying cause, and the presence of residual cardiac lesions. Echocardiography is frequently used to assess myocardial function during the weaning process. Weaning and separation from ECMO assist is accomplished with optimal ventilatory and inotropic support. When flow rates are approximately 20% of maximal support, the circuit is allowed to recirculate. After successful separation from ECMO, the cannulae are usually left in place for 1 h, flushed every 15 min, and subsequently removed if hemodynamic stability is maintained. In an open chest following decannulation, purse-string sutures remain in place and are snared.

2.2. Statistical analysis

Data are expressed as mean ± standard deviation (SD) or median with interquartile range (25—75 interquartile range (IQR)) for continuous variables and as frequencies and percentages for categorical variables. Continuous variables were compared by using the Mann—Whitney and Student’s t-tests, as appropriate. Fisher’s exact test and chi-square analyses were used for dichotomous and categorical variables. The probability of freedom from events was estimated according to the Kaplan—Meier method. Univariate analysis was carried out using a p-value of <0.05 between survivors and non-survivors. A receiver operating characteristics (ROC)/discriminant analysis was performed for each statistically significant continuous variable to determine the best criterion value (threshold) for predicting death or survival at last follow-up. For variables with accuracies ≥85%, p-values for comparing the proportions above the identified ROC thresholds were calculated using χ² or Fisher’s exact test. Due to small sample multivariate logistic regression model was not performed. Statistical Package for Social Sciences (SPSS 15.0.1) for Windows (SPSS Inc., Chicago, IL, USA) was used.

3. Results

3.1. Patients characteristics

Of 27 neonates receiving post-cardiotomy ECMO, 20 had FSV. Fourteen had ECPR. Ten underwent the Norwood operation (NO) for hypoplastic left heart syndrome (HLHS). Four had aortic atresia-mitral stenosis, four aortic atresia-mitral atresia, and two aortic stenosis-mitral stenosis HLHS variant. One had restrictive atrial septal defect prior to NO. Pulmonary blood flow reconstitution was established with right ventricle-to-pulmonary shunt (Sano) (n = 6) and mod-
Table 1. Demographic and clinical variables: comparison between ECPR survivors\(^a\) and non-survivors.

<table>
<thead>
<tr>
<th>Variables (total = 14)</th>
<th>ECPR non-survivors (N = 8)</th>
<th>ECPR survivors (N = 6)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
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<tr>
<td>Age at ECPR (days)(^a)</td>
<td>7.9 ± 2.9</td>
<td>7.6 ± 2.52</td>
<td>0.2</td>
</tr>
<tr>
<td>Weight at ECPR (kg)(^a)</td>
<td>3.51 ± 1.88</td>
<td>3.41 ± 1.71</td>
<td>0.2</td>
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<tr>
<td>Gender (M/F)</td>
<td>7/1</td>
<td>5/1</td>
<td>0.5</td>
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<tr>
<td>Diagnosis</td>
<td></td>
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<tr>
<td>HLHS</td>
<td>75%</td>
<td>67%</td>
<td></td>
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<tr>
<td>FSV (other than HLHS)</td>
<td>25%</td>
<td>33%</td>
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<tr>
<td>GS/CA</td>
<td>33%</td>
<td>0</td>
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<tr>
<td>Pre-ECPR</td>
<td></td>
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<tr>
<td>CPR duration(^a)</td>
<td>42.1 ± 7.7</td>
<td>38.6 ± 6.3</td>
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<tr>
<td>Timing of ECMO deployment</td>
<td>7 am–5.59 pm</td>
<td>63%</td>
<td>0.9</td>
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<tr>
<td>Location of cardiac arrest</td>
<td>87%</td>
<td>83%</td>
<td>0.9</td>
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<tr>
<td>Surgeon available on-site</td>
<td>63%</td>
<td>67%</td>
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<tr>
<td>Peak pH</td>
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<tr>
<td>≤7.19</td>
<td>13%</td>
<td>17%</td>
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<tr>
<td>7.2–7.34</td>
<td>75%</td>
<td>83%</td>
<td></td>
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<tr>
<td>&gt;7.35</td>
<td>12%</td>
<td>0</td>
<td></td>
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<tr>
<td>Serum peak lactate (mmol l(^{-1}))</td>
<td>12%</td>
<td>0</td>
<td>0.7</td>
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<tr>
<td>0–4.9</td>
<td></td>
<td>13%</td>
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<tr>
<td>5.0–9.9</td>
<td>75%</td>
<td>83%</td>
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<tr>
<td>&gt;10.0</td>
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<td>13%</td>
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<tr>
<td>Maximum VIS</td>
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<td></td>
<td>0.7</td>
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<tr>
<td>≤10</td>
<td>0</td>
<td>0</td>
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<td>11–14</td>
<td>12%</td>
<td>0</td>
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<td>15–19</td>
<td>13%</td>
<td>33%</td>
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<td>20–24</td>
<td>13%</td>
<td>17%</td>
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<tr>
<td>≥25</td>
<td>62%</td>
<td>50%</td>
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<tr>
<td>During ECPR</td>
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<tr>
<td>Peak pH (first 24 h)</td>
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<tr>
<td>≤7.19</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
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<tr>
<td>7.2–7.34</td>
<td>25%</td>
<td>50%</td>
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<tr>
<td>&gt;7.35</td>
<td>75%</td>
<td>50%</td>
<td></td>
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<tr>
<td>Serum peak lactate (first 24 h) (mmol l(^{-1}))</td>
<td>13%</td>
<td>17%</td>
<td>0.03</td>
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<tr>
<td>0–4.9</td>
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<td>13%</td>
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<td>75%</td>
<td>67%</td>
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<tr>
<td>&gt;10.0</td>
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<td>87%</td>
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<td>Maximum VIS (first 24 h)</td>
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<td>0.8</td>
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<tr>
<td>≤10</td>
<td>0</td>
<td>0</td>
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<tr>
<td>11–14</td>
<td>0</td>
<td>0</td>
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<td>15–19</td>
<td>50%</td>
<td>33%</td>
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<tr>
<td>20–24</td>
<td>37%</td>
<td>17%</td>
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<tr>
<td>≥25</td>
<td>13%</td>
<td>33%</td>
<td></td>
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<tr>
<td>Serum creatinine (first 72 h) (mg dl(^{-1}))</td>
<td>63%</td>
<td>50%</td>
<td>0.8</td>
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<tr>
<td>≤1.0</td>
<td></td>
<td>63%</td>
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<tr>
<td>1.1–1.6</td>
<td>0</td>
<td>50%</td>
<td></td>
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<tr>
<td>&gt;1.7</td>
<td>37%</td>
<td>0</td>
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<tr>
<td>SV function (first 48 h)</td>
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<tr>
<td>RV(_{nic})</td>
<td>37%</td>
<td>50%</td>
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<tr>
<td>RV(_{nic,1})</td>
<td>13%</td>
<td>17%</td>
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<tr>
<td>RV(_{nic,2})</td>
<td>50%</td>
<td>33%</td>
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<tr>
<td>Use of diuretics (hours following ECMO)</td>
<td>25%</td>
<td>33%</td>
<td>0.8</td>
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<tr>
<td>0–23</td>
<td>25%</td>
<td>33%</td>
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<tr>
<td>24–47</td>
<td>50%</td>
<td>50%</td>
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<tr>
<td>&gt;48</td>
<td>25%</td>
<td>17%</td>
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<tr>
<td>Negative fluid balance (days following ECMO)</td>
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<td>67%</td>
<td>0.7</td>
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<tr>
<td>0–1</td>
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<td>2–3</td>
<td>37%</td>
<td>67%</td>
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<tr>
<td>&gt;4</td>
<td>63%</td>
<td>33%</td>
<td></td>
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<tr>
<td>ECMO duration (days)(^b)</td>
<td>8 (5–11.5)</td>
<td>4 (3–6.5)</td>
<td>0.02</td>
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<tr>
<td>Post-ECPR</td>
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<tr>
<td>Peak pH (first 24 h)</td>
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<td>0.09</td>
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<tr>
<td>≤7.19</td>
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<tr>
<td>7.2–7.34</td>
<td>50%</td>
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</tr>
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<td>5.0–9.9</td>
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Table 1 (Continued)

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<td>0</td>
<td>0.8</td>
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<tr>
<td>Maximum VIS (first 24 h)</td>
<td>0</td>
<td>0</td>
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<td>33%</td>
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<tr>
<td>≥1.7</td>
<td>25%</td>
<td>33%</td>
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<tr>
<td>Use of diuretics (after ECMO decannulation)</td>
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<td>0.1</td>
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<tr>
<td>0–23</td>
<td>12%</td>
<td>50%</td>
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<tr>
<td>24–47</td>
<td>50%</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>≥48</td>
<td>38%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Negative fluid balance (after ECMO decannulation)</td>
<td></td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>0–1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2–3</td>
<td>37%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>63%</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

CPR: cardiopulmonary resuscitation; ECPR: extracorporeal cardiopulmonary resuscitation; FSV: functional single ventricle; GS/CA: genetic syndrome/chromosomal anomaly; HLHS: hypoplastic left heart syndrome; M/F: male/female; PSHU: Pediatric Surgical Heart Unit; SV: single ventricle; VIS: vasoactive inotropic score; and ECMO: extracorporeal membrane oxygenation.

Italics represent P values that are statistically significant (< 0.05).

* Mean ± SD.

b Median (25th to 75th quartile); all categorical variables are expressed frequencies or percentages.

Follow-up (mean interval 13.2 ± 3.3 months).

ified Blalock–Taussig shunt (mBTS) (n = 4). Four neonates had FSV other than HLHS. Three underwent Damus–Kay–Stansel (DKS) or modified NO (two Sano and one mBTS). Two (of three) were diagnosed with double-outlet right ventricle, mitral atresia, aortic atresia, and interrupted aortic arch and one with double-inlet left ventricle, transposed great arteries, hypoplastic aortic valve, and mitral atresia. The fourth neonate underwent aorto-pulmonary shunt with anomalous pulmonary venous connection (APVC) repair for unbalanced atrioventricular septal defect, pulmonary atresia, right isomerism, and obstructed APVC.

Two patients had extracardiac anomalies associated with chromosomal or genetic abnormalities (GS/CA). One was diagnosed with Turner’s and one with VACTERL – abnormalities of the vertebrae, anus, cardiovascular tree, trachea, esophagus, renal system, and limb buds – (and severe renal dysplasia) syndrome.

Patients ranged in age from 1 to 18 days. Mean age and weight were 7.8 ± 2.9 days and 3.44 ± 1.78 kg, respectively. Two patients had gestational age <35 weeks at birth and three weighted <2.5 kg at the time of surgical repair. Major indication for ECPR was acute cardiac arrest (86%) and respiratory failure followed by cardiac arrest (14%). ECPR was deployed in PSHU in 12 patients. Between 7 am and 6 pm, eight neonates required ECPR (vs six during weekends or weeknights (7 pm–6 am)). Transthoracic cannulation was

![Fig. 1. Post-cardiotomy rescue ECMO in neonates with complex single ventricle: Patient distribution and outcome. (a) Mean interval 13.2 ± 3.3 months. BTS: Blalock–Taussig shunt; DKS: Damus–Kay–Stansel operation; ECPR: extracorporeal cardiopulmonary resuscitation; FSV: functional single ventricle; HLHS: hypoplastic left heart syndrome; SPS: systemic-to-pulmonary shunt; TAPVC: total anomalous pulmonary venous connection; and TXP: transplantation.](https://academic.oup.com/ejcts/article-abstract/40/6/1396/420219)
used in 13 patients. The median interval between the beginning of CPR and the initiation of ECMO (CPR duration) was 39 min (IQR 26—52).

Demographic and clinical data for all patients treated with ECPR are depicted in Table 1.

3.2. Early results and hospital survival

The median duration of ECMO was 6 days (IQR 3—14). ECMO was successfully discontinued in all but three (79%) patients. All of these patients remained alive for at least 24 h after ECMO discontinuation. Eight (57%) patients survived to hospital discharge (Fig. 1). One of the non-survivors had a second ECMO run.

The causes for hospital mortality (often more than one) included multi-organ failure (MOFS) (n = 4, 29%), sepsis or necrotizing enterocolitis (NEC) (n = 5, 36%), intraventricular or cerebral hemorrhage (n = 2, 14%), and failure of cardiac recovery (n = 1, 7%). None suffered ischemic brain injury as manifested by clinical or imaging findings. There was one re-operation during ECMO for severe tricuspid valve insufficiency (NO-Sano) that required valvuloplasty. The patient suffered major intraventricular hemorrhage and ECMO support was withdrawn. Four more re-operations (two in the same patient) were performed off ECMO and prior to hospital discharge. One had shunt revision, one sternal deep wound infection, and one peritoneal dialysis catheter insertion. The latter suffered from NEC and had bowel resection. None survived hospital discharge. Both patients with G5/CA decannulated from ECMO but did not survive hospital discharge.

Five patients during ECMO and two after decannulation required ultrafiltration or peritoneal dialysis. Four did not survive hospital discharge (43% survival). Serum creatinine level (either within 72 h following ECMO or 24 h following decannulation from ECMO) was not statistically different between survivors and non-survivors (p = 0.8 and 0.8, respectively). Three non-survivors had serum creatinine >1.7 mg dl⁻¹ within 72 h following ECMO. In 63% of non-survivors, negative fluid balance was achieved in more than 72 h following ECMO. Patients that did not survive hospital discharge experienced the same trend achieving negative fluid balance after ECMO discontinuation.

There was echocardiographic evidence of ventricular recovery within 48 h following ECMO in 50% of survivors (vs 38% of non-survivors, p = 0.4). Fifty percent of patients with poor ventilator performance (RVnl-2) after 48 h following ECMO did not survive hospital discharge.

Fifty percent of ECPR survivors and 38% of non-survivors remained on mechanical ventilator support for more than 15 days (p = 0.5) with median ICU length of stay (ICULOS) 14 days (IQR 11.5–21.5) and 10 days (IQR8.5–20.5), respectively (p = 0.09).

Outcomes between ECPR survivors and non-survivors are summarized in Table 2.

3.3. Intermediate survival, time-related events, and need for heart transplantation

At last follow-up (median: 11 months (1234)) 43% of patients were alive and neurologically intact. Two patients died after hospital discharge. One died from NEC. Another patient died from acute shunt occlusion followed by cardiac arrest prior to arrival in the emergency room. Another required HTxP after stage II palliation due to severe heart failure and was alive at last follow-up. Freedom from death or HTxP at 1, 3, 6, and 12 months was 57.1 ± 13.2%, 50.2 ± 13.4%, 42.9 ± 14.2%, and 35.7 ± 14.9%, respectively (Fig. 2).

One survivor suffered transient ischemic cerebral event following stage II palliation. The patient recovered completely and is alive at last follow-up.
There were two re-operations after hospital discharge: one after modified NO-mBTS and one after NO-Sano had shunt revision prior to stage II palliation. Both patients were alive at last follow-up. Freedom from re-operation after ECMO decannulation (stage II and III palliation for FSV or HTxP excluded) at 1, 3, 6, and 12 months was 83.3 ± 15.2%, 66.7 ± 19.2%, 50.5 ± 20.4%, and 50.5 ± 20.4%, respectively (Fig. 3).

3.4. Risk factors for survival

Mean CPR duration between ECMO survivors and non-survivors was 38.6 ± 6.3 and 42.1 ± 7.7 min, respectively (p = 0.12). Median duration of ECMO between survivors and non-survivors was 4 days (IQR: 3–6.5) and 8 days (IQR: 5–11.5), respectively (p = 0.02) (Fig. 4).

Variables available before, during, and after rescue ECMO deployment were analyzed to determine statistical significance between survivors and non-survivors. From the 26 variables included, serum peak lactate levels within 24 h following rescue ECMO (p = 0.03) and ECMO duration (p = 0.02) were statistically significant between survivors and non-survivors (Table 1). Using ROC/discriminate analysis, serum peak lactate level within 24 h following ECMO at threshold value 8.9 mmol l⁻¹ was the most accurate continuous variable predictive of survival (area under the curve (AUC) 0.87 (0.617–1.094); sensitivity 87%; specificity 99%; accuracy 89%; p = 0.033) with lower lactate level being associated with survival benefit.

4. Discussion

ECMO survival for post-cardiectomy patients varies between different centers [16,17,19–21]. When ECMO is deployed during CPR efforts, outcomes are, often, poorer [10–17]. The use of ECMO to treat cardiac arrest refractory to routine resuscitative measures after complex repair in neonates with FSV has been reported, but results are based on few cases and not uniform in all patients with FSV.

Rescue ECMO is a potentially lifesaving intervention and the ultimate resort to reverse unfavorable outcome after surgical intervention for CHD, but one with relatively high morbidity and significant mortality. The most important factor for achieving favorable outcome with ECPR is the prompt establishment of adequate organ perfusion. The decision to institute ECMO support in infants and neonates, who have not responded to conventional CPR, must be made as early as efforts are initiated. It is our strategy to consider all candidates for ECPR after cardiectomy as long as there is witnessed arrest, with lack of recovery of cardiac function within 1 min of CPR and absence of co-existing conditions, such as pre-existing severe neurologic, end-organ injury, or genetic anomaly that will preclude survival. Once the decision is made, our target deployment time is within a short period of time (25–45 min).

This study intended, strictly, to focus on the subset of neonates with complex FSV (including HLHS) for whom rescue ECMO deployment was required after surgical intervention in the setting where cardiac arrest refractory to conventional CPR measures occurred outside the OR. It was not our intention to provide survival comparison analysis between patients with post-cardiectomy ECPR and those with cardiac arrest complicating other medical conditions where, as reported, survival difference might be present [3]. Survival analysis was undertaken and determinants of outcome assessed between survivors (favorable outcome) and non-survivors (non-favorable outcome).

While the results have improved in neonates following NO, poor outcomes were reported in other FSV subgroups, especially following obstructed APVC repair [16]. Furthermore, as reported [22], survival is extremely poor when patients were placed on extracorporeal support out of the OR. Early institution of ECMO support in the OR was associated with a better chance of survival to hospital discharge in patients with single-ventricle physiology. This indicates that neonates with FSV are more vulnerable to myocardial damage and less tolerant to any disturbance added to the demands of balancing two circulations and
adapting to an increased volume load. In our series, survival at hospital discharge was achieved in 57% of neonates. These results are favorably compared with those with post-cardiotomy non-ECMO patients [16,17,19,21,23].

As previously reported [14,20], CPR duration prior to ECMO deployment might not be associated with decreased survival. The duration of CPR was not statistically different between patients with favorable and unfavorable outcome in our series. Even though this study did not intend to evaluate CPR adequacy and the potential link of ineffective CPR performance to poor neurological or survival outcomes, quality and effectiveness of resuscitation and cerebral/somatic oxygen delivery, especially in neonates with compromised systemic-to-pulmonary shunts, are essential during all stages of urgent cannulation. More importantly, we identified three patients in whom chest compression was performed for more than 45 min (one had 68 min) prior to ECMO support who survived without any major ischemic cerebral insult. All of the patients in our study had a witnessed arrest with conventional CPR started promptly, indicating the importance of immediate and adequate resuscitation even if prolonged CPR efforts are needed in anticipation of ECMO deployment. By extension, patients having ineffective CPR might suffer cerebral ischemia or other end-organ damage, thereby increasing the likelihood for unfavorable outcome despite successful ECMO decannulation.

ECMO duration and impact on survival following ECPR remain controversial and results varied [16,17,19,22]. Consistent with other studies [11,16,17], ECMO duration was statistically different in the ECPR survivors compared with non-survivors. That might reflect high incidence of early withdrawal of support in those with severe end-organ injury after cardiac arrest. Furthermore, longer duration of extracorporeal support has widespread deleterious effects on end-organ systems, which may contribute to late mortality [24]. A significant number of our patients, who died after ECMO discontinuation, died of MOFS or sepsis. New strategies and innovative approaches might be critical to reduce the inflammatory response from ECMO and modify its detrimental impact on intermediate outcomes after hospital discharge.

Variables previously reported [2–7,17,19,21,23] that influence survival after non-rescue ECMO in post-cardiotomy patients are not always associated with poorer prognosis after ECPR [14,16,20]. Younger age, prematurity, laboratory values (such as low pH, elevated serum lactate, phosphorus, or creatinine levels), increased transfusion requirements, type of surgical repair (uni- vs bi-ventricular), urgent deployment of ECMO or prolonged support and emergence of complications (intracranial or pulmonary hemorrhage, MOFS or sepsis, and renal or hepatic failure) are, often, described as predictors of non-favorable outcome after ECMO in post-cardiotomy patients with FSV. As previously suggested [5,15–17,21], pH and serum lactate abnormal values reflect either the overall hypoperfusion state before deployment of ECMO or problems in oxygen delivery and extraction after deployment of ECMO. Our study indicates that peak serum lactate level (threshold value 8.9 mmol·l⁻¹) within 24 h following ECPR might predict unfavorable outcome. VIS has been evaluated in the past as a predictor of outcome. As others [3,6,17], we did not find any statistical association between high VIS (before, during, and after ECMO) and decreased survival. We value the use of bifrontal cerebral and somatic near-infrared spectroscopy as a crucial monitoring tool to guide pump-flow adjustment and inotropic support. Especially in neonates with FSV and open systemic-to-pulmonary shunts, sophisticated management to maintain optimal cerebral and body oxygen delivery/extraction and adequate end-organ perfusion is of the essence.

After ECPR is instituted, frequent echocardiographic evaluation is paramount in post-cardiotomy neonates for assessing the recovery rate of the ventricular function, identifying any residual lesion that may require re-intervention and, often, guiding effective management or the need for HTxP. We observed a clinical trend toward decreased survival in patients whose single ventricle continued to perform poorly after 48 h following ECMO, even though that did not reach statistical significance between ECPR survivors and non-survivors. ECMO withdrawal should not be attempted unless repair of residual lesion that is expected to have a hemodynamic impact in myocardial recovery takes place. In our study, only one patient underwent re-operation to address residual lesion but without favorable outcome.

Often, post-cardiotomy rescue ECMO may require prolonged duration of mechanical support due to failure of early recovery of cardiac function, which predisposes to development of major complications, such as sepsis, MOFS, intracranial hemorrhage, and coagulopathy, as observed in this series. Furthermore, myocardial recovery might not be possible despite prolonged support. Then, HTxP represents the only alternative choice for survival. In the current series, HTxP was not required for ECMO exit strategy. Need for transplantation was reserved only in one case later after hospital discharge due to progressive deterioration of the ventricular function.

Poor urine output in the first 24 h or renal dysfunction following ECMO represents a surrogate marker of organ perfusion and it has been shown to influence survival on ECMO and at hospital discharge, despite the use of hemodialysis [15,17,21]. Our findings indicated an adverse influence of renal dysfunction in hospital and overall morbidity, including end-organ recovery.

In neonates and infants receiving extracorporeal support, adverse neurological outcomes were reportedly present in more than one-third of survivors [7,8]. The incidence of neurologic complications was not statistically different between survivors and non-survivors in our study. Interestingly, it has been demonstrated [25] that the time for serum lactate to normalize on ECMO might be a risk factor for poor mental score at 2 years’ follow-up. Due to the small sample and relatively short follow-up period, no meaningful analysis of variables predicting poorer neurological outcome was possible in this study. The benefit from using induced mild core hypothermia, immediately after CPR efforts are initiated, is yet to be determined. We practice gradual rewarming process after the initial 24 h, targeting a core temperature of 36.5 °C or less at nearly 48 h after ECMO deployment. Follow-up and future analysis of this practice are needed to determine its significance on neurodevelopmental outcome.
Recent studies have linked bleeding and increased blood transfusion requirements to decreased hospital survival and substantial morbidity after ECMO [17,24]. Due to our conservative strategy, by judiciously escalating anticoagulation therapy within 48-h period following ECMO, major bleeding complications were limited in our series. Furthermore, meticulous surgical hemostasis, cell salvage during cannulation, use of polymethylpentene-hollow-fiber oxygenator, and miniaturization of ECMO circuit with smaller priming volume and heparin-bonded biocompatible surface coating can help reducing exposure to blood products.

The influence of GS/CA on clinical outcome did not reach statistical significance between survivors and non-survivors, even though both of neonates with GS/CA did not survive hospital discharge. This may be due to the small sample studied.

4.1. Study limitations

This series is subject to many limitations inherent in a single-site retrospective observational study, such as selection bias and lack of randomization. In addition, collection of variables is not under the control of investigator and, therefore, variables that could have had an important influence on outcome may not be available for analysis. Multiple medical providers were involved in the care of the patients and variations in medical therapy certainly occurred prior, during, and after ECMO support. There was no complete or uniform appraisal of neurologic function by an independent pediatric neurology specialist. Inasmuch as centers may have varying surgical approaches and ECMO management protocols, it is difficult to generalize these findings.

Due to small size, no comprehensive statistical analysis could be pursued to assess variables predicting or associated with selective morbid conditions linked to rescue ECMO. Finally, the relatively limited power of the study precluded logistic regression analysis to identify independent predictors of outcome.

In summary, it is well acknowledged that patients in need for extracorporeal support, who have undergone single-ventricle reconstruction, are at increased risk of hospital mortality. Despite the heavy toll in resources required, post-cardiomyotomy ECMO for neonates with complex FSV or HLHS and intractable cardiac arrest that occurs outside the OR carries a favorable outcome for more than half of the patients at hospital discharge. Given the interplay of many variables, the complexity of underlying anatomical substrates associated with congenital heart anomalies and the unique physiology of neonates with FSV, these findings should not be generalized to other patient population. In care facilities with structural proficiency and accuracy in effective and rapid ECMO deployment, aggressive strategy toward timely application of ECPR is justified in this subset of patients when no other morbid conditions that severely limit lifestyle or survival are present. Many of previously reported predictors of outcome after non-rescue conventional ECMO do not appear to influence survival in a rescue extracorporeal support. Instead, ECMO duration and serum peak lactate level following ECPR might influence survival after hospital discharge.

Expeditious ECMO deployment after proper patients’ selection, refinement of CPR quality, and use of adjunctive neuroprotective interventions, such as induced hypothermia, might further improve outcomes.

Prospective multi-site cohort studies with standardization of protocols and assessment of all variables should be encouraged to empower a comprehensive statistical analysis to determine incremental risk factors, help refining selection criteria, and determining suitability for rescue ECMO in post-cardiomyotomy patients with complex single ventricle, who suffered cardiac arrest refractory to conventional CPR strategies.

Acknowledgment

Special thanks to Mr Christopher Blair for providing the statistical analysis.

References

Appendix A. Conference discussion

Dr J. Fraga: Yes, this is what I am asking, because it is a different context. If any of these patients with shunt-dependent circulation goes down due to shunt insufficiency or occlusion, this is one thing. If the patient arrests because of primary myocardial or circulatory failure, it is a different issue and certainly another subset of patients, accounting for different results.

Dr Polimenakos: The vast majority of these patients had hemodynamic instability due to cardiac failure. We had two patients that had one complete occlusion and one near-complete occlusion of the shunt, and actually both of these patients went on ECMO and then had a re-operation for shunt revision. Both of them, unfortunately, did not survive to hospital discharge.

Mrs Wojtyla: Correct. I do not have a great answer for that. I am going to have to refer to Dr Polimenakos. I am sorry.

Dr Polimenakos: The vast majority of these patients had hemodynamic instability due to cardiac failure. We had two patients that had one complete occlusion and one near-complete occlusion of the shunt, and actually both of these patients went on ECMO and then had a re-operation for shunt revision. Both of them, unfortunately, did not survive to hospital discharge.

Dr Fraga: That is not stated in the paper, thank you. Now to my second question. In fact, I do not think that your policy regarding shunt management has been well addressed in your study. I know that you follow the 'open shunt' policy, which is the one that has been mostly accepted because of lung perfusion, but in most of the series, people have to control the shunts at some time: in up to 40% of cases, reducing the shunt, clipping it partially, or even occluding it. I am surprised that you have not experienced the need to control a shunt in any of your cases. Is that right?

Mrs Wojtyla: Correct.

Dr Fraga: Now, following that, my question raises the point that maybe in the cases where lactate clearance was low (and I underline the fact that this was the only variable associated with mortality), maybe you had too much of a shunt, I mean an excessive shunt flow that you could have improved by controlling the shunt while managing these patients. Do you understand my point?

Mrs Wojtyla: I do.

Dr Fraga: Maybe if you had a better control of the shunt flows, your results could be even better. Linked to this, maybe you had BT shunts and Sano shunts. I would like to know if you found any difference regarding the handling of these patients between these two types of shunts.

I enjoyed your paper. Your methodology is solid and useful. The clinical series is small and I do not think you can draw a lot of conclusions from the data.

Mrs Wojtyla: I just wanted to say that in all of our single-ventricle patients, when on rescue ECMO or putting them on ECMO, we tend to use a higher size cannula in order to facilitate higher pump flows, and that allows us to have a little bit better control over our systemic versus pulmonary flow.

Dr Fraga: Yes. And you play with the pulmonary vascular resistance.

Mrs Wojtyla: Correct.

Dr Fraga: But nevertheless, if you go into the literature, in up to 40% of the cases you will have to control the shunt at some stage. So I was wondering whether (because you did not need to control shunt flow in your series) in some of the patients in whom the blood lactate values did not go down, the contributing factor was possibly an excessive shunt flow and systemic hyperperfusion with escape to the lung circuit.

Dr Polimenakos: I just want to comment that I would argue about the need for occluding or partially occluding the shunt. I think maintaining antegrade flow through the shunt is very significant during ECMO support. That is why we utilize bigger sized cannulas. In addition, we did not demonstrate, and I think in the manuscript it might be more evident, that there is no difference between BT shunt or Sano shunt with respect to outcomes.